Remarks

Based on the amendments to the claims and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Status of the Claims

Claims 8-13, 56 and 70-75 are at issue and are present for examination. Claim 8 is the sole independent claim.

II. Summary of the Office Action

In the Office Action dated February 11, 2003, the Examiner made 5 rejections of the claims. Applicants respectfully offer the following remarks to overcome these rejections.

III. The Rejection of Claims 8-13, 56 and 70-75 Under 35 U.S.C. § 112, Second Paragraph Must be Withdrawn

At page 3 of the Office Action, claim 8 (and claims dependent thereupon 9-13, 56, and 70-75) was rejected as indefinite for lacking antecedent basis for the phrase "said template." Claim 8 has been amended to delete "template" and to substitute therefore the phrase "double-stranded DNA." Double-stranded DNA has antecedent basis in the preamble of the claim. Applicants respectfully request reconsideration and withdrawal of this rejection.

IV. The Rejection of Claims 8, 9, 10, 13, and 71-73 Under 35 U.S.C. § 102(b) as Being Anticipated by Davey et al. is Traversed Must be Withdrawn

In the Office Action at pages 3 and 4, claims 8, 9, 10, 13, and 71-73 were rejected under 35 U.S.C. §102(b) as being anticipated by Davey, *et al.* (United States patent no. 5,409,818, hereinafter "Davey"). Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim 8 is drawn to a method for synthesizing a nucleic acid molecule from a preparation comprising RNA and double-stranded DNA, said method comprising mixing the preparation with one or more DNA polymerases, and one or more peptides or polypeptides having ribonuclease activity, and incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of said double-stranded DNA and sufficient to degrade single-stranded RNA. Claims 9, 10, 13, and 71-73 depend—directly or indirectly—from claim 8 and, thus, include conditions sufficient to degrade single-stranded RNA.

A claimed invention is anticipated under 35 U.S.C. § 102 only if there is "[d]isclosure in a single piece of prior art of each and every limitation of a claimed invention." *Apple Computer, Inc. v. Articulate Systems, Inc.*, 234 F.3d 14, 20, 57 USPQ2d 1057, 1061 (Fed. Cir. 2000), *citing Electro Med. Sys. S.A. v. Cooper Life Sciences,* 34 F.3d 1048, 1052, 32 USPQ2d 1017, 1019 (Fed. Cir. 1994). Davey does not disclose conditions sufficient to degrade single-stranded RNA and, therefore, does not anticipate the present invention.

In support of this rejection, the Examiner alleges that:

> Davey et al. teach a nucleic acid amplification process which involves the synthesis of RNA and double stranded DNA in a single reaction medium containing reagents comprising multiple DNA

> polymerases and ribonuclease and incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule and sufficient to degrade single-stranded RNA.

Office Action, page 3.

Applicants respectfully disagree with the Examiner's assertion as the conditions disclosed in Davey are not sufficient to degrade single-stranded RNA. The ribonuclease used by Davey is "specific for RNA-DNA hybrids." Davey, column 5, lines 34-35. Further, Davey states "[e]ach enzyme or enzyme preparation should be free of deleterious ribonuclease ("RNase") activities, with the exception of the preferred addition of a ribonuclease activity which is specific for hybrids of RNA and DNA (for example, ribonuclease H)." Davey, column 7, lines 17-22. Thus, Davey does not teach conditions sufficient to degrade single-stranded RNA.

Applicants therefore respectfully submit that Davey fails to disclose at least one element of the present claims and, therefore, Davey does not anticipate the present claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

V. The Rejection of Claims 8, 9, 10, 13, and 72 Under 35 U.S.C. § 102(e) as Being Anticipated by Kenten et al. Must be Withdrawn

In the Office Action at pages 4 and 5, claims 8, 9, 10, 13, and 72 were rejected under 35 U.S.C. §102(e) as being anticipated by Kenten, *et al.* (United States patent no. 6,048,687, hereinafter "Kenten"). Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim 8 is drawn to a method for synthesizing a nucleic acid molecule from a preparation comprising RNA and double-stranded DNA, said method comprising mixing

the preparation with one or more DNA polymerases, and one or more peptides or polypeptides having ribonuclease activity, and incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of said double-stranded DNA and sufficient to degrade single-stranded RNA. Claims 9, 10, 13, and 72 depend—directly or indirectly—from claim 8 and, thus, require conditions sufficient to degrade single-stranded RNA.

A claimed invention is anticipated under 35 U.S.C. § 102 only if there is "[d]isclosure in a single piece of prior art of each and every limitation of a claimed invention." *Apple Computer, Inc. v. Articulate Systems, Inc.*, 234 F.3d 14, 20, 57 USPQ2d 1057, 1061 (Fed. Cir. 2000), *citing Electro Med. Sys. S.A. v. Cooper Life Sciences,* 34 F.3d 1048, 1052, 32 USPQ2d 1017, 1019 (Fed. Cir. 1994). Kenten does not disclose conditions sufficient to degrade single-stranded RNA and, therefore, does not anticipate the present invention.

In support of this rejection the Examiner alleges that

> the preparation taught by Kenten et al. comprises RNA and double-stranded DNA. It is noted that Kenten et al. teach the addition of a ribonuclease, and this is encompassed by claim 9 drawn to a number of specific ribonucleases, as well as fragments, variants derivatives or mutants thereof.

Office Action, page 4.

Applicants respectfully disagree with the Examiner's assertion as the conditions disclosed in Kenten are not sufficient to degrade single-stranded RNA. The ribonuclease used by Kenten "hydrolyses RNA of an RNA-DNA hybrid without hydrolysing single or double-stranded RNA or DNA." Kenten, column 4, lines 20-22. Kenten refers to several publications for a detailed description of the amplification process used. See, Kenten,

column 2, line 66, to column 3, line 4. One of these references (EP 0392 822-A2) is the European equivalent of the Davey patent discussed above. Thus, the amplification method of Kenten is the same as that of Davey and, similarly, does not disclose conditions sufficient to degrade single-stranded RNA.

Applicants therefore respectfully submit that Kenten fails to disclose at least one element of the present claims and, therefore, Kenten does not anticipate the present claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

VI. The Rejection of Claims 70, 74, and 75 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Davey et al. Must be Withdrawn

In the Office Action at pages 5-7, claims 70, 74, and 75 were rejected under 35 U.S.C. §103 as being obvious over Davey. Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 70, 74, and 75 depend from claim 8. As discussed above, claim 8 is drawn to a method for synthesizing a nucleic acid molecule from a preparation comprising RNA and double-stranded DNA, said method comprising mixing the preparation with one or more DNA polymerases, and one or more peptides or polypeptides having ribonuclease activity, and incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of said double-stranded DNA and sufficient to degrade single-stranded RNA.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). In pertinent part, the MPEP states

that "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." MPEP 2143.03, *citing In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). In addition, "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." MPEP 2143. Further, "[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion to make the proposed modification." MPEP 2143.01 *citing In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case for the obviousness of the presently claimed invention and respectfully request reconsideration and withdrawal of this rejection as it may be applied to the present claims.

As discussed above, Davey does not disclose conditions sufficient to degrade single-stranded RNA. There is no suggestion in Davey to modify the conditions in order to make them sufficient to degrade single-stranded RNA. Further, modifying the conditions of Davey so as to degrade single-stranded RNA would render Davey unsatisfactory for its intended purpose. The purpose of Davey is the amplification of specific nucleic acid sequences. Davey, Abstract. This is accomplished by converting a single-stranded RNA molecule into an double-stranded DNA molecule from which additional single-stranded RNA molecules can be transcribed. The transcribed single-stranded RNA molecules then serve as templates from which to produce additional double-stranded DNA molecules. See, Davey, Figure 1. In conditions sufficient to

degrade single-stranded RNA, the input single-stranded RNA would be degraded as would the transcribed single-stranded RNA and no amplification would occur. Modifying the conditions of Davey to conditions sufficient to degrade single-stranded RNA would render Davey unfit for its intended purpose; thus, there is no motivation to make such a modification of the conditions of Davey.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case for the obviousness of the presently claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

VII. The Rejection of Claims 8-12, 70, 71 and 73 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Major and Maudru et al. Must be Withdrawn

In the Office Action at pages 7-9, claims 8-12, 70, 71, and 73 were rejected under 35 U.S.C. §103 as being obvious over Major (*Biotechniques* 12(1):40-43, 1992, hereinafter "Major") and Maudru *et al.* (*J. Virological Methods* 66:247-261, 1997, hereinafter "Maudru"). Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim 8 is drawn to a method for synthesizing a nucleic acid molecule from a preparation comprising RNA and double-stranded DNA, said method comprising mixing the preparation with one or more DNA polymerases, and one or more peptides or polypeptides having ribonuclease activity, and incubating said mixture under conditions sufficient to synthesize a nucleic acid molecule complementary to all or a portion of said double-stranded DNA and sufficient to degrade single-stranded RNA. Claims 9-12, 70, 71, and 73 depend—directly or indirectly—from claim 8 and, thus, include one or more peptides having ribonuclease activity.

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). In pertinent part, the MPEP states that "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." MPEP 2143.03, *citing In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). In addition, "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." MPEP 2143. Further, when the teachings of a prior art reference are considered:

> A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied* 469 U.S. 851 (1984)

MPEP §2141.02

Major is cited as teaching a PCR method for screening point mutations. The Examiner characterizes Major as teaching that "some primers, especially those with 3'-terminal T:T mismatch result in extra minor bands when bacterial colony lysates were used for the starting material" resulting in a decrease in sensitivity of the assay. Office Action, paragraph bridging pages 7 and 8. The Examiner acknowledges that Major does not teach the inclusion of ribonuclease in a method of synthesizing nucleic acids. Office Action, page 8, lines 1 and 2.

Maudru is cited for the proposition that the background signal in a PCR-based RT assay is the result of an intrinsic RT activity of *Taq* DNA polymerase and that the

background may be eliminated by the inclusion of ribonuclease in the assay. Office Action, page 8, first full paragraph.

The Examiner then concludes:

> One of ordinary skill in the art at the time of filing would have been motivated to add a polypeptide with ribonuclease activity to the method taught by Major, in order to remove residual RNA sequence contamination from the targeted nucleic acid template in any preparation which would contain substantial amounts of RNA, such as a bacterial colony lysate, in order to decrease the level of background signal from the taught PCR assay. As the ordinary artisan would know that any nucleic acid preparation that has not been purified, such as a bacterial colony lysate, contains substantial amounts of contaminating RNA, the motivation for the removal of these contaminating sequences is that this would increase the sensitivity of the taught PCR assay method from bacterial colony lysates, thus eliminating the need for purification of the template DNA and reducing the time and work needed to perform the assay. This is supported by both Major, who teach that some primer sets when used with bacterial colony lysates result in extra minor bands, and Maudru et al. who teach that the background signals of PCR based nucleic acid synthesis reactions is due to an intrinsic RNA-dependent DNA polymerase activity of *Taq* DNA polymerase. The reasonable expectation of success for the inclusion of ribonuclease in the nucleic acid synthesis reaction of Major comes from the high degree of knowledge in the field of nucleic acid synthesis and the results of Maudru et al. who teach that the simultaneous addition of ribonuclease in order to eliminate background signals in the polymerase chain reaction mix containing *Taq* DNA polymerase did not adversely affect the synthesis of the desired nucleic acid products by PCR.

Office Action, pages 8 and 9.

Applicants respectfully submit that the Examiner has mis-characterized the teachings of Maudru; Maudru does not stand for the proposition that "background signals of PCR based nucleic acid synthesis reactions is due to an intrinsic RNA-dependent DNA polymerase activity of *Taq* DNA polymerase." Maudru is concerned with eliminating background reverse transcriptase activity in a PCR-based reverse

transcriptase activity. Maudru first conducts a reverse transcription reaction with a potentially reverse transcriptase-containing sample using a test RNA template and oligonucleotide primer that binds to the template. Maudru, pages 249-250, section 2.2.1. Any cDNA produced from the reverse transcription reaction is then amplified using PCR. Maudru, page 250, section 2.2.2. The reverse transcriptase activity of the polymerase used to conduct the PCR step causes the production of a cDNA during the PCR step that is not the result of the presence of an reverse transcriptase enzyme in the reverse transcription step. Maudru, page 256, left column and Figure 4. Thus, signals observed in the absence of reverse transcriptase in the sample "were due to the thermostable DNA polymerase being able to copy the RNA template during PCR." Maudru, page 256, sentence bridging columns. RNase is added by Maudru to prevent the production of a cDNA molecule by the DNA polymerase in the PCR amplification step. One skilled in the art, reading Maudru as a whole, would conclude that Maudru stands for the proposition that background reverse transcriptase activity can be eliminated in a reverse transcriptase assay by the degradation of template RNA prior to amplification. See, Maudru, page 258, section 4, second sentence.

One skilled in the art would have had no motivation to add RNase to the PCR amplification reaction of Major since there is no suggestion that RNA or reverse transcriptase has anything to do with the assay described in Major. Major describes a PCR based screening method for identifying point mutations. Major, page 40, sentence bridging columns one and two. Major uses DNA templates and primers (Major, page 40, column 2) not an RNA template and DNA primer combination that could be reverse transcribed. One skilled in the art would have had no reasonable expectation that

inclusion of RNase in a PCR reaction would have had any effect on a reaction conducted on a DNA template with a DNA primer. Under these conditions, reverse transcriptase activity of the DNA polymerase used to conduct the PCR reaction is simply not relevant since reverse transcriptase activity requires an RNA template and DNA primer.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case for the obviousness of the presently claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

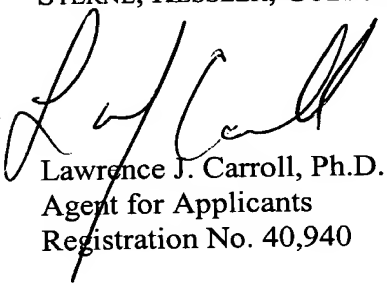
Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant(s) therefore respectfully request(s) that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant(s) believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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